DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/10/2010 has been entered.

Applicant's arguments filed 09/10/2010 have been fully considered. The claim amendment and the newly added claims dated 09/10/2010 has been entered. Claims **1, 3-18, 20-22** are pending and under consideration. Claims 2 and 19 have been canceled.

Claim Rejections - 35 USC § 112/Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **8-9, 10**, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims **8-9** recites the limitation "in a state of adhesion". There is insufficient antecedent basis for this limitation in the claim.

Claim **10** recites the term "a state of adhesion". It is unclear as to the metes and bounds of what would be considered "in a state of adhesion".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims **8, 10, 13 and 17** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require functionally ingredients equivalent to the conditioned medium that is conditioned by astrocytes. The specification fails to provide any characteristics of said medium. However, the genus of "functionally ingredients equivalent to the conditioned medium", which, when constructed and used as claimed, lacks a written description, and as such, there is no indication that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification, and are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the claimed invention in a detailed drawing, or by describing the invention with sufficient, relevant, identifying characteristics (as it relates to the claimed invention as a whole), such that one of skill in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the breath of the genus of "a functionally equivalent preliminarily prepared medium to a medium that is conditioned by astrocytes lacks a written description. The specification provides no guidance to what types of cell(s) that would be used in order to produce the functionally equivalent media, and the specification teaches that there is no guarantee that every conditioned medium of every GFAP positive cells (i.e., astrocytes)

can be used to culture neurons stably for a long time or to induce differentiation of ES cells to neural cells. See ¶161 of the specification.

The skilled artisan cannot envision the detailed chemical structure of all of the functionally equivalent media that are encompassed by the claims, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention, and a reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim **22** is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

In the instant case, the recitation of the limitation "wherein said primate embryonic stem cells do not express nestin" (newly added claim 22) is considered new matter. Applicants in their arguments dated 09/10/2010, page 10 argue that nestin is a well known marker for neural stem cell, and undifferentiated embryonic stem cells are NOT reactive for nestin (See Specification, Figure 23, col. 1, page 5, line 23, and page 44, line 14). Thus, the embryonic stem cells of the instant claims are not equivalent to the precursor cells of Example 8 of Weiss, and are certainly not the progeny of neural

stem cells (arguments dated 09/10/2010, page 10, last paragraph) for the specific support of the negative limitation for a primate embryonic stem cells that do not express nestin. However, upon further review of the instant specification, examiner could not find support for primate embryonic stem cells that do not express nestin culturing in suspension.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed…If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendment made to the disclosure".To the extent the claimed primate embryonic stem cells do not express nestin are not described in the instant disclosure, claim 22 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not teach primate embryonic stem cells that do not express nestin according to claim 1 that is adequately described in the specification. In this case, it appears that the claims reflect a genus of primate embryonic stem cells that do not express nestin. The newly added claim 22 and claim 1 as amended the primate embryonic stem cells require a functional negative characteristics that is these cells do not express nestin. A review of art would indicate that many cell type do not express nestin, however, they clearly are not primate embryonic stem cells. For example, **Li et al** (Journal of Cell Science 123: 853-860,

2009) teaches that that c-KIT-positive melanoblasts are non-pigmented, Tyrp1-positive and nestin-negative cells from murine skin (p 858, 2nd column) Simply providing, for what the cell dos not have would constitute an enormous amount of experimentation to empirically test all these cells to determine if they are primate embryonic stem cells that do not express nestin. The specification does not provide any guidance on determining what is included or excluded by the claims as amended and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Claim **8-10, 13, 15, 17, and 18** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

In the instant case, the recitation of the limitation "in the absence of basic fibroblast growth factor (bFGF) and/or epidermal growth factor (EGF)" (amended claims 8-10) is considered new matter. However, upon further review of the instant specification, examiner could not find support for primate SCS cultured in the absence of basic fibroblast growth factor (bFGF) and/or epidermal growth factor (EGF).

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed…If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on U.S.C. 112, first

paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendment made to the disclosure".To the extent the claimed culturing said stem cell spheres (SCS) "in the absence of basic fibroblast growth factor (bFGF) and/or epidermal growth factor (EGF)" are not described in the instant disclosure, the above claims are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not teach culture of SCS in the absence of bFGF and/or EGF that is adequately described in the specification. In this case, it appears that the claims reflect a genus of primate SCS that culturing said stem cell spheres in the absence of bFGF and/or EGF. The said claims require culture of primate SCS "in the absence of basic fibroblast growth factor (bFGF) and/or epidermal growth factor (EGF)". A review of art would indicate that many cell type do not require bFGF and/or EGF for culture, however, they clearly are not primate SCS. For example, **Li et al** (Journal of Cell Science 123: 853-860, 2009) teaches that human dermal stem cells (DSCs) grown in suspension and unlike the previous studies using medium containing bFGF and EGF, defined to grow neural stem cells, we used human embryonic-stem-cell-based medium conditioned with mouse embryonic fibroblasts (p 858, 1st column, last paragraph). Simply providing, for what the cell does not have would constitute an enormous amount of experimentation to empirically test all these cells to determine if they are primate embryonic stem spheres that do not require bFGF and/or EGF in culture. The specification does not provide any guidance on determining what is included or excluded by the claims as amended and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 3-4, 8-12, 13-18 under 35 U.S.C. 103(a) as being unpatentable over Tropepe et al (Neuron, 30: 65–78, April, 2001); Weiss et al, (US 5,981,165) in view of Suemori et al (Developmental Dynamics, 222: 273–279, 2001) is withdrawn in view of the amendment to the claims dated 09/10/2010.

The rejection of claims 5-7 under 35 U.S.C. 103(a) as being unpatentable over Tropepe et al Neuron, 30: 65-78, April, 2001); Weiss et al, (US 5,981,165) in view of Vitkovic et al. (AIDS Res and Human Retroviruses, 7(9): 723-727, 1991) when taken with Reubinoff et al. (Nature Biotechnology, 19:1134-1140, 2001 (IDS)) when taken with Thomson et al. (Science, 282:1145-1147, 1998) is withdrawn in view of the amendment to the claims dated 09/10/2010.

Claim Rejections - 35 USC § 103/Necessitated by Amendment

Claims 1, 3, 7, 10-12, 16, 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Itskovitz-Eldor et al** (Mol Med, ;6(2): 88-95., 2000); **Reubinoff et al.** (US 2002/0068045) in view of **Suemori et al** (Developmental Dynamics, 222: 273–279, 2001 (IDS)); **Dhandapani *et al.*** (**The J. of Biol. Chem.**, 278(44): 43329-43339, 2003 (IDS)); **Totey et al.** (US 2006/01211109).

Itskovitz-Eldor et al (Mol Med, ;6(2): 88-95., 2000) teach culturing human embryonic stem cells in suspension to induce their differentiation into embryoid bodies (EBs) (abstract). Human ES cells can reproducibly differentiate in vitro into EBs comprising the three embryonic germ layers. Itskovitz-Eldor teach the ability to induce formation of human embryoid bodies that contain cells of neuronal origin will be useful in studying early human embryonic development

as well as in transplantation medicine (abstract). In addition, **Reubinoff et al.** (US 2002/0068045) teach a method of differentiating and obtaining a pure population of neural precursor cells from human ES cells comprising steps of propagating undifferentiated ES cells on mouse embryonic fibroblast (MEF) feeder layers forming colonies/clumps of cells, isolating the clumps or clusters of cells cultured in serum free medium supplemented with EGF and bFGF both at 20 ng/ml, which are turned into round spheres (spheroid bodies or embryoid bodies (EB); the term "spheroid bodies" is considered the same as EB) in suspension culture (floating culture) (Example 5). Itskovitz-Eldor taken with Reubinoff does not specifically teach culturing Cynomolgus primate embryonic stem cells **(claims 7, 10-12).** Reubinoff et al. teach "6-8 days after initial plating, ICM like clumps were removed mechanically by a micropipette from differentiated cell outgrowths and replated on fresh feeder layer. The resulting colonies were further propagated in clumps of about 100 stem cell-like cells, on mouse feeder layer, about every 7 days. The clumps were either dissociated mechanically, or with a combined approach of mechanical slicing followed by exposure to dispase mechanical dissociation of clusters of cells grown on feeder layer from the initial culture of ICM-like cells" (par. 338) **(claim 21).**

However, at the time the claimed invention was made, **Suemori et al** teach the derivation of ES cell lines from the rhesus monkey (*Macaca mulatta*) and common marmoset (*Callithrix jacchus*) with shared many characteristics with human ES cells (p 274, 1st column, 1st paragraph) **(claim 11**). **Suemori et al** teach because the cynomolgus monkey, as well as the rhesus monkey, belong to the Catarrhini, which are closely related to humans, and because they are widely used for medical research, cynomolgus monkey ES cells would be valuable for preclinical research before the clinical usage of human ES cells and such ES cells could be maintained for long periods as stem cells, and they showed differentiation in vitro and in vivo

into various tissues indicating their pluripotency (p 274, 1st column, 1st paragraph) **(claims 3, 16).** Sumeori teaches the cells were cryopreserved (p 274 2nd column bridges to p 275) **(claim 12).** Suemori suggest the cynomolgus ES cell lines established will provide a good model system for development of transplantation therapies using human ES cells (p 278, 2nd column). In addition, Suemori the autonomous appearance of differentiated cells during ES culture reduced when FBS was replaced by knockout serum replacement (KSR) medium and in such serum-free medium cynomolgous ES cells could be maintained in the undifferentiated state for longer periods (p 274, 2nd column) **(claim 22).**

Suemori does not specifically teach culturing the Cynomolgus ES cells in an astrocyte conditioned medium.

However, at he time of the instant invention **Dhandapani *et al.*** (**The J. of Biol. Chem.**, 278(44): 43329-43339, 2003 (IDS)) teach the production of astrocyte-conditioned media and the culture of neurons in the astrocyte-conditioned media (Abstract and p. 43330, Materials). Dhandapani teaches that both soluble and insoluble factors produced from the astrocytes in the astrocyte conditioned medium play a mediatory role in astrocyte-induced neuroprotection (p 43329, 2nd column, 2nd paragraph) thus astrocytes can protect neurons from serum-deprivation-induced cell death (abstract).

Totey et al. also teach that bFGF and EGF are differentiation agents encouraging differentiation of neuronal cell types (par. 78).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): “Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art

elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to try bFGF, EGF in serum supplemented differentiated medium taught by Totey et al. for the method of Itskovitz-Eldor et al /Reubinoff et al. to differentiate EB to neural precursor cells. Since the EB of Itskovitz-Eldor et al/ Reubinoff et al. can be differentiated into neural precursor cells, and the differentiation medium of Totey et al. is intended for differentiating EBs into neural cell type, thus a person of ordinary skill in the art would try and/or substitute the method step of using the differentiation medium of Totey et al. for the same purpose in the method of Itskovitz-Eldor et al/Reubinoff et al. with a reasonable expectation of success. Although of Itskovitz-Eldor et al/ Reubinoff et al discusses producing neural donor cells in the context of neural transplantation therapy, one of skill in the art would readily recognize that an unlimited source of astrocytes would also be useful to produce astrocyte-conditioned medium to protect neurons from serum deprivation-induced cell death, as noted by Dhandapani. This is further underscored by the teachings of Suemori who suggests the cynomolgus ES cell

lines established will provide a good model system for development of transplantation therapies using human ES cells (p 278, 2nd column).

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

A. Applicants argue that Suemori is cited only for the "deficiency of culturing primate embryonic stem cells and not for the stage of differentiation of the SCS." (Office Action, page 9) Applicants do not dispute that Suemori teaches the culture of primate embryonic stem cells and the cryopreservation of the cells resulting from those cultures. However, Applicants submit that the combined references do not teach the suspension culture of embryonic stem cells in an astrocyte conditioned medium. As the Examiner has conceded that the Suemori reference does not speak to this element, Applicants submit that the addition of Suemori to Tropepe and Weiss does not remedy the deficiencies of Tropepe and Weiss. The arguments have been fully considered but are not persuasive.

To the extent that Sumeori is used in the instant rejection for the culture of primate embryonic stem cells and the cryopreservation of the cells resulting from those cultures as discussed above in the newly applied rejection, therefore Applicant's arguments are not convincing.

B. Applicants argue the presently claimed invention presents unexpected results. Applicants submit that even if the Examiner had successfully established a prima facie case of obviousness, the results of the presently claimed method are unexpected. The presently claimed methods generate stem cell spheres, and an isolated population of desirable cells in large numbers. Applicants argue specifically, the present method generates a large number of neural stem cells from the total population of embryonic stem cells, in a short period of time, which can then produce an isolated population of a specific type of neuron (e.g., dopaminergic neuron, GABAergic neuron, or a cholinergic neuron), or glial cells. (Specification, page 3, lines

7-8, page 15, lines 5-12, 18-20). In a stem ceil sphere, by day 4 of suspension culture, 100% of the cells express nestin (See Specification, Figure 24, described at page 14, lines 17-22, and page 62, lines 8-16, describing the amount of mRNA for nestin, which is expressed in neural stem cells and neurons, divided by the amount of GAPDH, which is expressed by all cells). By day 2 of adhesion culture after suspension culture (step B and B'), all of the cells also expressed TH (an indicator of a differentiated neuron). (Id.) The arguments have been fully considered but are not persuasive.

Regarding the generation of stem cell spheres, and an isolated population of desirable cells in large numbers, as discussed above in the newly applied rejection although of Itskovitz-Eldor et al/ Reubinoff et al discusses producing neural donor cells in the context of neural transplantation therapy, one of skill in the art would readily recognize that an unlimited source of astrocytes would also be useful to produce astrocyte-conditioned medium to protect neurons from serum deprivation-induced cell death, as noted by Dhandapani. This is further underscored by the teachings of Suemori who suggests the cynomolgus ES cell lines established will provide a good model system for development of transplantation therapies using human ES cells (p 278, 2nd column).

Claims 1, 4-6, 8-9, 13-15, 17-18 are under 35 U.S.C. 103(a) as being unpatentable over Itskovitz-Eldor et al (Mol Med, ;6(2): 88-95., 2000); Reubinoff et al. (US 2002/0068045) in view of Suemori et al (Developmental Dynamics, 222: 273–279, 2001); Dhandapani *et al.* (The J. of Biol. Chem., 278(44): 43329-43339, 2003); Totey et al. (US 2006/01211109) and further in view of **Zhang et al,** [Nature Biotechnology, 19: 1129-1133, 2001, (IDS)].

The teachings of Itskovitz-Eldor et al/Reubinoff et al/Suemori et al/Dhandapani *et al*/Totey et al apply here as indicated above.

Itskovitz-Eldor et al/Reubinoff et al/Suemori et al/Dhandapani *et al*/Totey et al do not specifically teach the step, further comprising (B') culturing said stem cell sphere (SCS) in the state of adhesion of SCS to an adhesive culture substratum comprising a cell adhesion molecule in the absence of basic fibroblast growth factor (bFGF) and/or epidermal growth factor (EGF) and in the presence of an astrocyte conditioned medium or ingredients equivalent to the conditioned medium, thereby obtaining a neuron.

However, at the time of the instant invention Zhang teaches human embryonic stem (ES) cell-derived neural precursors generate all three CNS cell types in vitro and the isolated neural precursors expanded as free-floating cell aggregates in a suspension similar to "neurosphere" cultures (p 1129, 2nd column last paragraph). Zhang et al teach upon aggregation of embryoid bodies (EBs), differentiating ES cells formed large numbers of neural tube-like structures in the presence of FGF-2, wherein neural precursors within these formations were isolated and purified on the basis of differential adhesion (abstract). Zhang et al teach following withdrawal of FGF-2 they differentiated into neurons, astrocytes and oligodendrocytes (abstract). Zhang teaches the in vitro differentiation of the ES cell-derived neural precursors was induced by withdrawn of FGF-2 and plating on the state of adhesion of the neural stem cell precursor by plating on ornithine and laminin substrate (p 1130, 1st column, 2nd paragraph). After 7-10 days after plating differentiated neurons expressed neuronal markers MAP2ab, β_{III}-tubulin, GABA, tyrosine hydroxylase (TH), GFAP (p 1130, 2nd column, 1st paragraph). Zhang teaches the suspension of human ES in ingredients substantially equivalent to an astrocyte conditioned medium and the absence of EGF (p 1132-1133 and figure 3). Zhang teaches on a pragmatic level, the in vitro generation of neural tube-like structures and the possibility of isolating these structures on the basis of their differential adhesion provides a simple yet efficient approach for generating human ES-derived neural precursors in high purity (p 1131, 2nd column, 3rd

paragraph). Zhang suggests because undifferentiated ES cells and precursors to other lineages may form tumors and foreign tissues, the generation of purified somatic populations of cells is a key prerequisite for the development of ES cell-based neural transplant strategies (p 1131, 2nd column, 3rd paragraph). Zhang teaches the chemically defined culture system they described provides an opportunity to explore the effects of single factors on human neuroepithelial proliferation and specification in vitro (p 1131, 2nd column, last paragraph).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

It would have been obvious for the person of ordinary skill in the art at the time the invention was made to try the method step of Zhang et al. to form SCS from EBs, and then

dissociate the SCS and culturing them in adherent (monolayer) culture. This is because that the method of Zhang et al. is considered as a known option for differentiating EBs into neural precursor cells. It is understood that upon the further culturing of EBs of Itskovitz-Eldor et al/Reubinoff et al/Suemori et al/Dhandapani *et al*/Totey et al SCS are inherently formed from the spheres as taught by Zhang et al. (p.1130, left col.). Thus, a person of ordinary skill in the art would certainly try the method of Zhang et al. to form SCS from EBs and then differentiate the cells dissociated from the SCS via the method of Itskovitz-Eldor et al/Reubinoff et al/Suemori et al/Dhandapani *et al*/Totey et al into neural cells inherently expressing neuron cell markers while the embryonic stem cells inherently are nestin negative.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAGDALENE SGAGIAS whose telephone number is (571)272-3305. The examiner can normally be reached on Monday-Friday, 9-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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